REMARKS

Claims 6, 7, 20, 24, 27 and 30-32 are active. Claims 8, 9, 21-23, 25, 26, 28 and 29 have been withdrawn from consideration. Claim 24 has been placed in independent form, since this claim was indicated as being allowable if it included the limitations of the claims from which it depended. Claim 20 has been amended as suggested by the Examiner. Accordingly, the Applicants do not believe that any new matter has been added. Favorable consideration and allowance of this application is now respectfully requested.

Request that the Finality of the Official Action be Withdrawn

The last Official Action was made first-action-FINAL. However, new prior art (e.g., Hiromitsu, JP 363267255A and Suekawa et al.) has been applied and new grounds of rejection added (e.g., under 35 U.S.C. 103 and on obviousness-type double patenting grounds). This is the first notice that Applicants have had regarding this new prior art and these new rejections and they have not yet had an opportunity to respond. Accordingly, the Applicants respectfully request that the finality of the last Official Action be withdrawn.

Election/Restriction

The Applicants previously elected Group II (method of treatment) and the a species of compound for use in the elected method comprising (A) chlorogenic acid and (B) a central nervous system stimulating component. The Restriction Requirement has been made FINAL.

On June 2, 2005 the Applicants were required to further elect a single species of component (B) and subsequently elected (B) zingerol which is a heat component of ginger (*Zingiberaceae*). The claims as directed to the elected species (A) chlorogenic acid + (B) zingerol have been found in condition for allowance except for formal matters. Since

zingerol falls within the subgenus of isolated heat component of *Zingiberaceae* described in Claim 6, the Applicants respectfully request that heat components related to zingerol from this subgenus be examined.

Rejection—35 U.S.C. § 112, second paragraph

Claim 20 was rejected under 35 U.S.C. 112, second paragraph, as indefinite. This rejection is moot in view of the amendment above which defines the degree of hotness of the heat components by reference to heat components exemplified in the specification.

Rejection—35 U.S.C. § 103

Claims 30-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 in view of Hiromitsu, JP 363267255A (English Abstract). Examination encompasses the previously elected species (zingerol + isolated chlorogenic acid) and the currently elected species (capsaicin + isolated chlorogenic acid). This rejection concerns the previously elected species.

Cheng, Table 1 on page 579, refers to the effects of chlorogenic acid and the Abstract indicates that "chlorogenic acid. . .at higher doses possessed the delay (sic) hypotensive effect". Table 1 shows the effect of chlorogenic acid on arterial blood pressure of spontaneously hypertensive rats. However, Cheng does not disclose zingerol or combination of chlorogenic acid with zingerol.

Hiromitsu was cited as disclosing that "ginger liquid" (not necessarily containing zingerol) is useful "for depressing blood pressure". However, this statement appears anecdotal and there are no examples of the effects of ginger liquid as produced by the method described in the abstract on hypertension. Thus, this document does not provide a reasonable expectation of success for treating hypertension using ginger liquid. Moreover, there is no

suggestion in Hiromitsu to combine ginger liquid with isolated chlorogenic acid to treat hypertension.

On the other hand, Example 2 of the specification shows the anti-hypertensive activity of such a combination.

Moreover, one with ordinary skill in the art would not reasonably expect that a complex mixture of ingredients of Hiromitsu and chlorogenic acid would necessarily exhibit any effect on hypertension since the interaction of the Hiromitsu "ginger liquid" composition with chlorogenic acid could negate or inhibit the effects observed by Cheng. Common drug interactions include pharmacodynamic (where one drug competes for the same receptor site as another) and pharmacokinetic (where the absorbtion, distribution, metabolism or excretion of one drug is affected by the presence of another). For example, it is commonly known that consumption of grapefruit juice inhibits the uptake or activity of many drugs (see Oesterheld, previously submitted). Due to complexity of the mixture of Hiromitsu and the possibility of drug interactions which negate the hypertensive effects of chlorogenic acid of Cheng (or alternatively, those of the Hiromitsu composition) one with ordinary skill in the art would not have had a reasonable expectation of success in treating hypertension by merely combining the products of Cheng and Hiromitsu. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—35 U.S.C. § 103

Claims 6, 7, 20 and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 and Suekawa et al., Nippon Yakurigaku Zasshi 88:339 (English Abstract).

Cheng has been discussed above and describes the effects of chlorogenic acid on blood pressure in spontaneously hypertensive rats (see Table 1), but indicates that

chlorogenic acid had a delayed effect on reducing blood pressure ("the maximal effect was not observed until at least 50 min after the drug injection", middle of page 578).

Suekawa indicates that capsaicin 0.1 mg/kg caused a "rapid fall in blood pressure" followed by marked pressor responses (i.e., marked increases in blood pressure) in rats.

Since the effect of chlorogenic acid is delayed and capsaicin produces a delayed pressor effect, one with ordinary skill in the art would not have had a reasonable expectation of success from the cited prior art that the combination of these two substances would have operated together to treat hypertension. In fact, since Suekawa reports that capsaicin produced a delayed pressor effect, it teaches away from combining these two substances, since one with ordinary skill in the art would have expected that the delayed pressor effect would have antagonized the delayed antihypertensive activity reported by Cheng. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. § 103

Claim 20 was rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 and Hsia et al., U.S. Patent No. 6,440,464. This rejection is moot in view of the amendment of Claim 20.

Moreover, there is no suggestion in either Cheng or Hsia to combine chlorogenic acid and capsaicin, nor is there any reasonable expectation that this combination of ingredients would exert a superior antihypertensive effect. As evidenced by Suekawa, which is discussed above, one with ordinary skill in the art would have not had a reasonable expectation of success for combination of these ingredients due to the reported pressor effect exhibited after the administration of capsaicin and the delayed antihypertensive effect of chlorogenic acid administration as disclosed by Cheng. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—Obviousness-type Double Patenting

Claim 20 was rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending U.S. Applications 09/922,694, 10/826,289, 10/632,810, 10/810,611, or 11/106,428, in view of Hsia, U.S. Patent No. 6,440,464.

The cited copending U.S. patent applications were indicated to be directed to methods involving use of chlorogenic acid to treat hypertension. However, no mention is made of the combination of chlorogenic acid and capsaicin.

Hsia et al., U.S. Patent 6,440,464, discloses a complex mixture of ingredients only one of which is capsaicin. While commercially obtained capsaicin is described in col. 4, lines 53-59, there is no suggestion in Hsia for treating hypertension using capsaicin. Thus, there is no suggestion for a method of administering a composition which "consists essentially of chlorogenic acid and capsaicin". In fact, Hsia teaches away from a method using such a composition by disclosing that the novelty of his composition lies in a complex combination of ingredients, see Hsia, col. 3, lines 33-37. Furthermore, the disclosure of Hsia is prophetic even with respect to the complex mixtures disclosed by that patent. While col. 4, lines 1-3, indicates an object of the invention is to provide compositions that will lower blood pressure, there are no examples of the claimed compositions actually reducing blood pressure. Thus, the Hsia patent merely alleges that the claimed compositions treat cardiovascular disease, but provides no evidence that they do.

Even were there some general motivation to treat hypertension by modifying the methods in the copending claims by incorporating other components, such as capsaicin, Hsia does not disclose the equivalence of capsaicin for this purpose, nor provide a reasonable expectation of success that administering a composition consisting essentially of chlorogenic

acid and capsaicin would actually treat hypertension. Hsia does not suggest that the combination of chlorogenic acid and a heat component, such as zingerol or capsaicin, would be effective for treating hypertension. On the other hand, the inventors have discovered this combined effect and it is shown by Example 2 of the specification.

There is no reasonable expectation of success in the prior art for the combined effect, since chlorogenic acid and capsaicin have completely different chemical structures and unlike mixing compounds with similar structures and known functions, these diverse chemical structures provide no reasonable expectation of success for an additive or synergistic effect between them. Thus, with ordinary skill in the art would not reasonably expect that a complex mixture of ingredients of Hsia and chlorogenic acid would necessarily exhibit any reductive effect on hypertension since the interaction of the Hsia composition with chlorogenic acid could antagonize, have no effect, or agonize the effects observed for chlorogenic acid.

Moreover, the Hsia mixture contains components which are known to antagonize the effects of certain drugs. For example, it is commonly known that consumption of grapefruit juice inhibits the uptake or activity of many drugs (see Oesterheld, previously cited) and Hsia, in fact, indicates that grapefruit juice (col. 7, lines 37-43), as well as other complex and potentially suspect juices and herbal components are integral components of his mixture. Furthermore, those with skill in the medical and pharmacological arts recognize the unpredictability of the effects of administering different types of drugs or biologically active substances at the same time, see the commentary on the adverse effects of administering different drugs together on pages 21-23 of the Principles of Internal Medicine, 16th edition, McGraw Hill, New York (2005)(attached). Commonly known drug interactions include pharmacodynamic (where one drug competes for the same receptor site as another) and pharmacokinetic (where the absorption, distribution, metabolism or excretion of one drug is

affected by the presence of another). Moreover, coffee extracts containing chlorogenic acid are known to inhibit the absorption of other drugs, see excerpt from The PDR of Herbal Medicines (attached) and capsaicin is a well-known irritant that increases mucous secretion that could also affect drug adsorption.

Therefore, due to complexity of the mixture of Hsia and the possibility of drug interactions between the Hsia mixture and chlorogenic acid which would negate the hypertensive effects of chlorogenic acid one with ordinary skill in the art would not have had a reasonable expectation of success in treating hypertension by combining chlorogenic acid and the capsaicin ingredient disclosed by Hsia.

Since Hsia does not suggest treating hypertension by administering a composition consisting essentially of chlorogenic acid and capsaicin, nor provide any reasonable expectation of success for using this combination to treat hypertension, the Applicants respectfully request that this provisional rejection now be withdrawn.

Provisional Rejection—Obviousness-type Double Patenting

Claims 6, 7, 20 and 27 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending U.S. Applications 09/922,694, 10/826,289, 10/632,810, 10/810,611, or 11/106,428, in view of Suekawa et al., Nippon Yakurigaku Zasshi 88:339.

The Applicants traverse this provisional rejection since Suekawa indicates that capsaicin does not produce a sustained effect in lowering blood pressure, but instead produces an immediate fall followed by a pressor effect which raises blood pressure. Therefore, Suekawa does not provide evidence that addition of capsaicin to the chlorogenic acid based methods in the cited applications would have been an obvious variation. Instead,

Suekawa shows the unpredictability of the effects of the administration of capsaicin, since it results in a rise in blood pressure after the initial fall.

Should these provisional rejections be maintained, the Applicants respectfully request that they be held in abeyance pending the identification of otherwise allowable subject matter in the present application, see MPEP 804(I)(B).

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Thomas M. Cunningham
Registration No. 45,394

Customer Number
22850
(703) 413-3000
NFO:TMC:krs

Characteristics: Flowers have a strong fragrance and taste when rubbed.

Habitat: The plant is found in central and northern Europe, Asia, and North America.

Production: True Scurvy-Grass is the fresh flowering herb of Cochlearia officinalis annuals.

Other Names: Scrubby Grass, Spoonwort

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Glucosinolates: in the freshly-harvested, unbruised plant, chief components glucocochlearin, yielding with the destruction of the cells secretions of butyl mustard oil, besides among others glucotropaeolin (yielding butyl mustard oil) and sinigrin (yielding allyl mustard oil).

Flavonoids

Tropane alkaloids: tropine, m-hydroxybenzoyl-tropine (cochlearin)

Vitamin C

EFFECTS

Externally irritates the skin, due to the presence of mustard oils in the drug, in ethereal oil and in an ethanol solution.

INDICATIONS AND USAGE

Scurvy grass is used internally for Vitamin C deficiency, "blood-cleansing or purification" cures, gout, diuretic, rheumatism, stomach ache, and externally, as a poultice. A spirit made from scurvy-grass is used for skin irritations and as a mouthwash for gum diseases.

Efficacy has not been proven.

PRECAUTIONS AND ADVERSE REACTIONS

Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded. The administration of higher dosages can lead to mucous membrane irritations of the gastrointestinal tract.

DOSAGE

Mode of Administration: Alcoholic extracts of Scurvy grass are used topically. Freshly pressed juice is for internal use.

LITERATURE

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Cocoa

See Theobroma Cacao

Coffea Arabica

Coffee

DESCRIPTION

Medicinal Parts: The medicinal parts of the plant are the seeds in various forms and stages.

Flower and Fruit: The inflorescences are axillary dense clusters with 10 to 20 flowers. The sessile or very short pedicled partial inflorescences bear dense, overlapping apical leaves. The calyx is 2.5 to 3 mm long with a blunt 5-tipped border. The corolla is white and fragrant. The stamens come from the mouth of the tube and are exserted. The ripe fruit is elliptoid and shows flattened in cross-section, 12 to 18 mm long by 12 to 15 mm wide and has a 3 to 6 mm long stem. It is initially green, later yellow and dark red when ripe. The exocarp is tough, the mesocarp is fleshy and slightly sweet. The endocarp is hard. The seeds are convex with a groove on one side. They are 8 to 12 mm long, 5 to 8 mm wide and 3 to 5 mm thick. They are gray-green when fresh and brown after roasting.

Leaves, Stem and Root: Coffea arabica is an evergreen shrub or small tree up to 8 m high with many basal branches. The young branches are glabrous and flattened and nodes produce many shoots. The bark of the fruiting branches is ashy white. The leaves live for 2 to 3 years; are 6 to 20 cm long and 2.5 to 6 cm wide. They are glabrous, slightly coriaceous, dark green, glossy, elliptoid-lanceolate with a distinct leaf tip.

Habitat: Supposedly indigenous to Ethiopia, cultivated in many tropical regions.

Production: The coffee charcoal is produced by roasting outer seed parts of green, dried fruit, until almost black, and then grinding. The coffee beans are ripe for harvest nine months after flowering. Thereafter, they are processed using one of two methods. In the dry method, the fruit is dried for 3 to 4 weeks in the sun, or mechanically with air-stream dryers. In the wet method, the beans are placed in a water-filled tank, where the ripe ones sink to the bottom, and all remaining ones float on top. The ripe fruit is then mechanically crushed and subsequently fermented. Fermentation lasts for approximately 48 hours (for arabica varieties). Afterwards the coffee is dried in the sun, or mechanically, but this is unusual.

Not To Be Confused With: Coffeae Semen is not easily confused with other drugs. However, ground and roasted coffee may be mixed with coffee substitutes, such as: chicory, dandelion root, figs, sugar beet root, lupin seeds, rye kernels, and barleycorn.

Other Names: Arabica Coffee, Arabian Coffee, Caffea

ACTIONS AND PHARMACOLOGY

COMPOUNDS: COFFEAE CARBO

Purine alkaloids: main alkaloid caffeine

Trigonelline

Carbonisation products of hemicelluloses

EFFECTS: COFFEAE CARBO

Absorbent and astringent.

COMPOUNDS: COFFEAE SEMEN

Purine alkaloids: main alkaloid caffeine (0.6 - 2.2 %), with it theobromine, theophylline

Caffeic and ferulic acid ester of quinic acid: in particular chlorogenic acid

Trigonelline

Norditerpene glycoside ester

In roasted coffee beans: numerous aromatic substances yielded from carbohydrates, proteins, fats and aromatic acids through pyrolysis

EFFECTS: COFFEAE SEMEN

Coffee has the stimulatory effect on the central nervous system (CNS) and gastric secretions. It also increase the psychomotor stamina.

INDICATIONS AND USAGE

COFFEAE CARBO

- Diarrhea
- Inflammation of the mouth and pharynx

Coffee is used for nonspecific, acute diarrhea, and local therapy of mild inflammation of the oral and pharyngeal mucosa. In folk medicine coffee is also used for festering wounds.

COFFEAE SEMEN

Most of the indicated effects of coffee are due to the presence of caffeine. The primary effects of caffeine can be summarized as follows:

Caffeine has a positive inotropic effect. In higher concentrations, it has a positive chronotropic effect on the heart and CNS. It causes a relaxation of the smooth muscles of blood vessels (except for cerebral blood vessels) and the bronchial tubes. Moreover, caffeine works as a short-lived diuretic and produces an increase of gastric secretions and the release of catecholamines.

Caffeine works competitively to block adenosinal receptors which lie on cell surfaces in the brain, fat tissue, liver, kidneys, heart, and erythrocytes.

Heart, circulation, vessels: People who normally do not drink coffee, react 1 hour after an intake of 250 gm, with an increase of 10 mm Hg in their systolic blood pressure. Habitual coffee drinkers are tolerant in this regard.

Blood: After 9 weeks of an average daily intake of 5.6 cups of coffee (steeped for 10 min.), the overall and LDL cholesterol increases significantly. The use of coffee filters can reduce this by up to 80%.

Digestive tract: Oral intake of 200 mg of chlorogene acid doubles gastric secretion, as does caffeine alone.

Miscellaneous: A diet consisting of 20% green coffee, impedes the growth of DMBA induced tumors in hamsters by 90%.

Outcome of the stimulating effects of caffeine commence a few minutes subsequent to taking the drug. The maximum plasma concentration of caffeine is reached between 15 and 45 minutes later. The plasma half-life amounts to 4 to 6 hours.

The coffee extracts made from roasted and unroasted seeds are used analogously with other drugs containing caffeine for physical and mental fatigue. The drink can also be used therapeutically in cases of hypotonia, as an analeptic agent, in the treatment of influenza (flu) and migraine, as an additive to analgesia.

In folk medicine coffee is also used to increase performance capability.

PRECAUTIONS AND ADVERSE REACTIONS

COFFEAE CARBO

General: Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded.

Drug Interactions: The drug can hinder the resorption of other medicines.

COFFEAE SEMEN

General: Health risks following the proper administration of designated therapeutic dosages are not recorded. Quantities corresponding to up to 500 mg caffeine daily (5 cups of coffee) spread out over the day are toxicologically harmless for healthy adults accustomed to drinking coffee. Caution is advised for persons with sensitive cardiovascular systems, kidney diseases, hyperfunction of the thyroid gland, higher disposition to convulsions and certain psychic disorders, for

example panic anxiety states. Side effects of coffee intake, mainly caused by its chlorogenic acid content, can include hyperacidity, stomach irritation, diarrhea, reduced appetite. The first signs of poisonings are vomiting and abdominal spasms. Non-specific symptoms such as restlessness, irritability, sleeplessness, palpitations, dizziness, vomiting, diarrhea, loss of appetite, and headache appear with the long-term intake of dosages exceeding 1.5 gm caffeine/day. Caffeine can lead to psychic as well as physical dependency (caffeinism). Symptoms of withdrawal can include headache and sleeping disorders.

Pregnancy: Pregnant women should avoid caffeine, under no circumstances exceeding a dosage of 300 mg/day (3 cups of coffee spread out over the day).

Nursing Mothers: Infants whose nursing mothers take drinks containing caffeine may suffer from sleeping disorders.

OVERDOSAGE

Higher dosages lead to stiffness, arrhythmic spasms of different muscle groups, opisthotonus and arrhythmic tachycardia. Fatal poisonings with the drug are not conceivable. The lethal dosage (LD50) for an adult is approximately 150 to 200 mg caffeine/kg body weight (for which 50 kg body weight = 7.5 gm = 75 cups of coffee), although there are cases of survival also with 106 gm caffeine. The death of a child following the intake of 5.3 gm of caffeine has been reported. The therapy for caffeine poisoning should begin with the inducement of vomiting or gastric lavage. Afterwards activated charcoal and sorbitol to retard resorption should be given. Spasms are to be treated with diazepam.

DOSAGE

COFFEAE CARBO

Mode of Administration: Powdered coffee charcoal and its preparations intended for internal consumption or local application.

Daily Dosage: The average daily dose for internal use is 9 gm of ground drug. The average single dose is 3 gm of powder.

Storage: It should be stored in well-sealed containers.

COFFEAE SEMEN

Mode of Administration: The ground beans are used in different types of infusion, i.e. cooked coffee (filter, espresso etc.). Caffeine is used in various combinations and preparations for various therapeutic uses.

Preparation: The dried seeds are roasted until they procure a deep brown color and a characteristic aroma. This process is usually carried out in the country of consumption. During roasting, the beans float for 1.5 to 3 minutes in hot gas at 220°C to 270°C.

Storage: The beans should be stored in sealed containers away from light.

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Coffee

See Coffea Arabica

Cola Acuminata

Cola

DESCRIPTION

Medicinal Parts: The seeds are the medicinal parts of the plant.

Flower and Fruit: The male flowers with a diameter of 1.5 cm or the androgynous flowers with a diameter of 2.5 cm are axillary or on branches in cymes of few flowers. The 5 part calyx is white to yellow and marked red on the inside. The star-shaped fruit have 5 coriaceous, dark brown, up to 20 cm long and 5 cm wide and thick, unkeeled follicles arranged at right-angled to the stem. There are up to 14 ovate or square seeds of about 2.5 diameter in 2 rows with a white fleshy seed shell and usually reddish or red occasionally white seed kernal.

Leaves, Stem and Root: The plant is an evergreen tree 15 to 20 m tall. The trunk is branched down as far as the base. The old bark breaks off in pieces. The bark is dark green and rough. There are leaves only at the ends of the branches. They are 15 to 18 cm long and 10 cm wide, elliptoid to ovate, ending in a curled and spiralled tip, tough coriaceous, both sides are dark green and glossy.

Habitat: The plant is indigenous to Togo, Sierra Leone and Angola; found today in all tropical regions and cultivated widely.

Production: Ripe fruit is harvested, the seeds removed and dried in large piles. Cola nut consists of the endosperm freed from the testa of various Cola species, particularly Cola nitida.

Not To Be Confused With: Other varieties of Cola, such as Male kola which contains no caffeine.

Other Names: Kola Tree, Guru Nut, Cola Nut, Cola Seeds, Bissy Nut

ACTIONS AND PHARMACOLOGY

COMPOUNDS

Purine alkaloids: main alkaloid caffeine (0.6 - 3.7%), additionally theobromine, theophylline

(+)-catechin, (-)-epicatechin

Catechin tannins

Oligomeric proanthocyanidins

Starch

EFFECTS

A strong CNS stimulant; in animal tests: analeptic, stimulates production of gastric acid, lipolytic, increases motility; in humans: respiratory analeptic, stimulates gastric acid, lipolytic, increases motility, mildly positively chronotropic, and mildly diuretic.

INDICATIONS AND USAGE

■ Lack of stamina

Cola is used in mental and physical fatigue. In folk medicine it is used for tiredness, chewed to suppress hunger, thirst, morning sickness, and migraine; ground in poultices for wounds and inflammations; it is an indigenous cult drug.

PRECAUTIONS AND ADVERSE REACTIONS

Health risks following the proper administration of designated therapeutic dosages are not recorded. Side effects that may occur include difficulty falling asleep, hyperexcitability, nervous states of restlessness and stomach complaints. Signs of poisoning following the intake of cola drinks (20 to 60 mg caffeine per glass) or medications or stimulants containing cola extracts are hardly conceivable (Coffeae semen). Small children should avoid the intake of larger quantities of cola drinks. No administration should be carried out in the presence of stomach or duodenal ulcers, due to the drug's stimulation of gastric juice secretion.

DOSAGE

Mode of Administration: Powdered drug and other galenic preparations are for internal use.

Preparation: Dry extract: from the percolation 1:1 with 45% ethanol; Fluid extract: percolation with 70% ethanol (V/V); Cola tincture: 1:5 with 70% ethanol; Cola wine: 50 parts fluid cola extract with 850 parts Xeres wine and 100 parts sugar syrup.

Daily Dosage: Two to 6 gm of cola nut; 0.25 to 0.75 gm of cola extract; 2.5 to 7.5 gm of cola liquid extract; 10.0 to 30.0 gm of cola tincture; 60.0 to 180.0 gm of cola wine.

Storage: Cola should be protected from light in sealed containers.

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MONTVALE, NEW JERSEY

(Table 3-1). Codeine is biotransformed by CYP2D6 to the potent active metabolite morphine, so its effects are blunted in PMs and exaggerated in ultrarapid metabolizers. With beta blockers metabolized by CYP2D6 (including ophthalmic timolol and the antiarrhythmic propafenone), PM subjects display greater signs of beta blockade (including bradycardia and bronchospasm) than EMs. Further, in EM subjects, propafenone elimination becomes nonlinear at higher doses so, for example, a tripling of the dose may lead to a tenfold increase in drug concentration. The oral hypoglycemic agent phenformin was withdrawn because it occasionally caused profound lactic acidosis; this likely arose as a result of high concentrations in CYP2D6 PMs. Ultrarapid metabolizers may require very high dosages of tricyclic antidepressants to achieve a therapeutic effect, and with codeine may display transient euphoria and nausea due to very rapid generation of morphine.

The PM phenotype for CYP2C19 is common (20%) among Asians, and rarer (3 to 5%) in European-derived populations. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with "standard" dosages were markedly lower in EM patients (29%) than in PMs (100%). Thus, understanding the importance of this polymorphism would have been important in developing the drug, and knowing a patient's CYP2C19 genotype should improve therapy.

There are common allelic variants of *CYP2C9* that encode proteins with loss of catalytic function. These variant alleles are associated with a requirement for lower maintenance dose of warfarin. In rarer (<2%) individuals homozygous for these variant alleles, maintenance warfarin dosages may be difficult to establish, and the risk of bleeding complications appears increased. Similarly, patients with loss-of-function CYP2C9 alleles display increased rates of neurologic complications with phenytoin and of hypoglycemia with glipizide.

VARIABILITY IN THE MOLECULAR TARGETS WITH WHICH DRUGS INTERACT As molecular approaches identify specific gene products as targets of drug action, polymorphisms that alter the expression or function of these drug targets—and thus modulate their actions in patients—are also being recognized. For example, genome-wide searches in families with premature Alzheimer's disease have associated variants in the *APOE* locus with the disease (Chap. 350). The *E4* allele of the gene has been associated with a worse prognosis, a finding that has been attributed to reduced expression of choline acetyltransferase. Further, this polymorphism is also linked to response to the acetylcholinesterase inhibitor tacrine; a beneficial response appears to be more common in patients with the prognostically more benign *APOE2* or *APOE3* alleles (in which the target molecule is expressed more abundantly).

Multiple polymorphisms identified in the β_2-adrenergic receptor appear to be linked to specific phenotypes in asthma and congestive heart failure, diseases in which β_2-receptor function might be expected to determine prognosis. Polymorphisms in the β_2-receptor gene have also been associated with response to inhaled β_2-receptor agonists, while those in the β_1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering. Similarly, response to the 5-lipoxygenase inhibitor zileuton in asthma has been linked to polymorphisms that determine the expression level of the 5-lipoxygenase gene. Herceptin, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the herceptin receptor; thus, "genotyping" the tumor is a mechanism to avoid potentially toxic therapy in patients who would derive no benefit.

Drugs may also interact with genetic pathways of disease, to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks (Chap. 337). Deficiency of glucose-6-phosphate dehydrogenase (G6PD), most often in individuals of African or Mediterranean descent, increases risk of hemolytic anemia in response to primaquine and a number of other drugs that do not cause hemolysis in patients with adequate quantities of this enzyme (Chap. 93). Patients with mutations in the ryanodine receptor that controls intracellular calcium in skeletal muscle and other tissues may be asymptomatic until exposed to certain general anesthetics, which trigger the syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes (Chap. 214), and in some patients this adverse effect represents unmasking of previously subclinical congenital long QT syndrome.

POLYMORPHISMS THAT MODULATE THE BIOLOGIC CONTEXT WITHIN WHICH THE DRUG-TARGET INTERACTIONS OCCUR The interaction of a drug with its molecular target is translated into a clinical action in a complex biologic milieu that is itself often perturbed by disease. Thus, polymorphisms that determine variability in this biology may profoundly influence drug response, although the genes involved are not themselves directly targets of drug action. The common insertion/deletion (I/D) polymorphism in the ACE gene determines prognosis in many types of heart disease, including heart failure. In patients with heart failure treated with β-adrenergic blockers, the best response to therapy has been associated with the DD genotype, the group with the worst prognosis. The mechanism underlying this outcome is uncertain, but a direct effect of beta blockers on ACE seems unlikely; rather the I/D genotype likely affects the biology of heart failure to allow an improved response to beta blockers. Similarly, polymorphisms in genes important for lipid homeostasis (such as the ABCA1 transporter and the cholesterol ester transport protein) modulate response to HMG-CoA reductase inhibitors. In one large study, the combination of diuretic use combined with a variant in the adducin gene (encoding a cytoskeletal protein important for renal tubular sodium absorption) decreased stroke or myocardial infarction risk, while neither factor alone has an effect. Common polymorphisms in ion channel genes that are not themselves the target of QT-prolonging drugs may nevertheless influence the extent to which those drugs affect the electrocardiogram and produce arrhythmias.

PROSPECTS FOR INCORPORATING GENETIC INFORMATION INTO CLINICAL PRACTICE These and many other examples of associations between specific genotypes and drug responses raise the tantalizing prospect that patients will undergo routine genotyping for loci known to modulate drug levels or response prior to receiving a prescription. The twin goals are to identify patients likely to exhibit adverse effects and those most likely to respond well. Obstacles that must be overcome before this vision becomes a reality include replication of even the most compelling associations, demonstrations of cost-effectiveness, development of readily useable genotyping technologies, and ethical issues involved in genotyping. While these barriers seem daunting, the field is very young and evolving rapidly. Indeed, one major result of understanding of the role of genetics in drug action has been improved screening of drugs during the development process to reduce the likelihood of highly variable metabolism or unanticipated toxicity (such as torsades de pointes).

INTERACTIONS BETWEEN DRUGS

Drug interactions can complicate therapy by adversely increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels. *Interactions must be considered in the differential diagnosis of any unusual response occurring during drug therapy.* Prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A meticulous drug history should include examination of the patient's medications and, if necessary, calls to the pharmacist to identify prescriptions. It should also address the use of agents not often volunteered during questioning, such as over-the-counter (OTC) drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. The practicing physician cannot be expected to memorize these. How-

TABLE 3-2 *Drugs with a High Risk of Generating Pharmacokinetic Interactions*

Drug	Mechanism	Examples
Antacids; bile acid sequestrants	Reduced absorption	Antacids/tetracyclines; cholestryamine/digoxin
Proton pump inhibitors; H_2-receptor blockers	Altered gastric pH	Ketoconazole absorption decreased
Rifampin; carbamazepine; barbiturates; phenytoin; St. John's wort; glutethimide	Induction of hepatic metabolism	Decreased concentration and effects of: warfarin; quinidine; cyclosporine; losartan
Tricyclic antidepressants; fluoxetine; quinidine	Inhibitors of CYP2D6	Increased beta blockade; decreased codeine effect
Cimetidine	Inhibitor of multiple CYPs	Increased concentration and effects of: warfarin; theophylline; phenytoin
Ketoconazole, itraconazole; erythromycin; clarithromycin; calcium channel blockers; ritonavir	Inhibitor of CYP3A	Increased concentration and toxicity of: some HMG-CoA reductase inhibitors; cyclosporine; cisapride, terfenadine (now withdrawn)
		Increased concentration and effects of: indinavir (with ritonavir);
		Decreased clearance and dose requirement for: cyclosporine (with calcium channel blockers)
Allopurinol	Xanthine oxidase inhibitor	Azathioprine and 6-mercaptopurine toxicity
Amiodarone	Inhibitor of many CYPs and of P-glycoprotein	Decreased clearance (risk of toxicity) for: warfarin; digoxin; quinidine
Gemfibrazol (and other fibrates)	CYP3A inhibition	Rhabdomyolysis when co-prescribed with some HMG-CoA reductase inhibitors
Quinidine; amiodarone; verapamil; cyclosporine; itraconazole; erythromycin	P-glycoprotein inhibition	Risk of digoxin toxicity
Phenylbutazone; probenecid; salicylates	Inhibition of renal tubular transport	Salicylates → increased risk of methotrexate toxicity

ever, certain drugs consistently run the risk of generating interactions, through mechanisms that are well understood; examples (not an exhaustive listing) are presented below and in Table 3-2. When such drugs are started or stopped, prescribers must be especially alert to the possibility of interactions.

PHARMACOKINETIC INTERACTIONS CAUSING DIMINISHED DRUG DELIVERY TO TARGET SITES ■ Impaired Gastrointestinal Absorption Aluminum ions, present in antacids, can form insoluble chelates with the tetracyclines, preventing their absorption. Kaolin-pectin suspensions bind digoxin, and when the substances are administered together, digoxin absorption is reduced by about one-half. Resins that sequester bile acids in the gut can bind other drugs, such as digoxin. Ketoconazole is a weak base that dissolves well only at acidic pH. Histamine H_2 receptor antagonists and proton pump inhibitors reduce gastric acidity and thus impair the dissolution and absorption of ketoconazole.

Induction of CYP or Transporter Activity Expression of some genes responsible for drug elimination, notably *CYP3A* and *MDR1*, can be markedly increased by "inducing" drugs, such as rifampin, carbamazepine, phenytoin, St. John's wort, and glutethimide and by smoking, exposure to chlorinated insecticides such as DDT (CYP1A2), and chronic alcohol ingestion. One mechanism for this coordinate induction of multiple pathways is increased expression of common transcription factors (e.g., hepatocyte nuclear factor 4α). Administration of inducing agents lowers plasma levels over 2 to 3 weeks as gene expression is increased. This alters the effects of many drugs, including warfarin, quinidine, mexiletine, verapamil, ketoconazole, itraconazole, cyclosporine, dexamethasone, methylprednisolone, prednisolone (the active metabolite of prednisone), oral contraceptive steroids, methadone, and metronidazole. These interactions all have obvious clinical significance. Further, if a drug dose is stabilized in the presence of an inducer which is subsequently stopped, major toxicity can occur as clearance returns to preinduction levels and drug concentrations rise. This is a particular problem with narrow-therapeutic-ratio drugs such as warfarin and some antiarrhythmics. Individuals vary in the extent to which drug metabolism can be induced, likely through genetic mechanisms.

Inhibition of Cellular Uptake or Binding Tricyclic antidepressants, doxepin, and chlorpromazine are potent inhibitors of norepinephrine uptake into adrenergic neurons and prevent the uptake of the guanidinium antihypertensive agents (such as guanethidine and guanadrel), thereby abolishing their antihypertensive effects. Similarly, the antihypertensive effect of clonidine is partially antagonized by tricyclic antidepressants.

PHARMACOKINETIC INTERACTIONS CAUSING INCREASED DRUG DELIVERY TO TARGET SITES ■ Inhibition of Drug Metabolism Inhibition of drug metabolism can lead to reduced clearance, prolonged half-life, accumulation of drug during maintenance therapy, and thus adverse effects. In contrast to induction, new protein synthesis is not involved, and the effect develops as drug and any inhibitor metabolites accumulate (a function of their elimination half-lives). Since shared substrates of a single enzyme can compete for access to the active site of the protein, many CYP substrates can also be considered inhibitors. However, some drugs are especially potent as inhibitors (and occasionally may not even be substrates); it is in the use of agents of the latter type that clinicians must be most alert to the potential for interactions.

Cimetidine (but not other H_2-receptor blockers) is a potent inhibitor of the oxidative metabolism of many drugs, including warfarin, quinidine, nifedipine, lidocaine, theophylline, and phenytoin. Severe adverse reactions can develop as a consequence.

The antifungal agents ketoconazole and itraconazole are potent inhibitors of enzymes in the CYP3A family. When fluconazole levels are elevated as a result of higher doses and/or renal insufficiency, this drug can also inhibit CYP3A. The macrolide antibiotics erythromycin and clarithromycin inhibit CYP3A4 to a clinically significant extent, but azithromycin does not. Some of the calcium channel blockers, including diltiazem, nicardipine, and verapamil can also inhibit CYP3A, as can some of the enzyme's substrates, such as cyclosporine. Examples of CYP3A substrates also include quinidine, lovastatin, simvastatin, atorvastatin, nifedipine, lidocaine, erythromycin, methylprednisolone, carbamazepine, midazolam, and triazolam.

Phenytoin, an inducer of many systems including CYP3A, inhibits CYP2C9. CYP2C9 metabolism of losartan to its active metabolite is inhibited by phenytoin, with potential loss of antihypertensive effect.

Accumulation of the prokinetic drug cisapride and the antihistamine terfenadine due to CYP3A inhibition led to QT prolongation and torsades de pointes. Measures to prevent co-prescription of these agents with CYP3A inhibitors were unsuccessful, and alternative safer agents were developed, so these drugs were eventually withdrawn.

Cyclosporine can cause serious toxicity when its metabolism via CYP3A4 is inhibited by erythromycin, ketoconazole, diltiazem, nicardipine, or verapamil. The risk of myopathy with some HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin) is thought to be increased by CYP3A4 inhibition. One agent in this class, cerivas-

tatin, was withdrawn because of an especially high incidence of this adverse effect, although cellular studies suggest inhibition of other pathways may have also contributed in this case. The antiviral ritonavir is a very potent CYP3A4 inhibitor that is often added to anti-HIV regimens not because of its antiviral effects but because it decreases clearance, and hence increases efficacy, of other anti-HIV agents. Grapefruit (but not orange) juice inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.

CYP2D6 is markedly inhibited by quinidine and is also blocked by a number of neuroleptic drugs, such as chlorpromazine and haloperidol, and by fluoxetine. The analgesic effect of codeine depends on its metabolism to morphine via CYP2D6. Thus, quinidine reduces the analgesic efficacy of codeine in EMs. Since desipramine is cleared largely by metabolism via CYP2D6 in EMs, its levels are increased substantially by concurrent administration of quinidine, fluoxetine, or the neuroleptic drugs that inhibit CYP2D6. Clinical consequences of fluoxetine's interaction with CYP2D6 substrates may not be apparent for weeks after the drug is started, because of its very long half-life and slow generation of a CYP2D6-inhibiting metabolite.

6-Mercaptopurine, the active metabolite of azathioprine, is metabolized not only by TPMT but also by xanthine oxidase. When allopurinol, a potent inhibitor of xanthine oxidase, is administered with standard doses of azathioprine or 6-mercaptopurine, life-threatening toxicity (bone marrow suppression) can result.

Inhibition of Drug Transport The best studied example is P-glycoprotein (Fig. 3-4). Quinidine inhibits P-glycoprotein function in vitro, and it now appears that the long-recognized doubling of plasma digoxin when quinidine is coadministered reflects this action in vivo, particularly since the effects of quinidine (increased digoxin bioavailability and reduced renal and hepatic secretion) occur at the sites of P-glycoprotein expression. Many other drugs also elevate digoxin concentrations (e.g., amiodarone, verapamil, cyclosporine, itraconazole, and erythromcyin), and a similar mechanism seems likely. Reduced CNS penetration of multiple HIV protease inhibitors (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein-mediated exclusion of the drug from the CNS; thus inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS.

A number of drugs are secreted by the renal tubular transport systems for organic anions. Inhibition of these systems can cause excessive drug accumulation. Salicylate, for example, reduces the renal clearance of methotrexate, an interaction that may lead to methotrexate toxicity. Renal tubular secretion contributes substantially to the elimination of penicillin, which can be inhibited (to increase its therapeutic effect) by probenecid.

Inhibition of the tubular cation transport system by cimetidine decreases the renal clearance of dofetilide and of procainamide and its active metabolite NAPA.

DRUG INTERACTIONS NOT MEDIATED BY CHANGES IN DRUG DISPOSITION Drugs may act on separate components of a common process to generate effects greater than either has alone. For example, although small doses of aspirin (<1 g daily) do not alter the prothrombin time appreciably in patients who are receiving warfarin therapy, aspirin nevertheless increases the risk of bleeding in these patients because it inhibits platelet aggregation. Thus the combination of impaired functions of platelets and of the clotting system, while useful in some patients, also increases the potential for hemorrhagic complications. Similarly, the use of other anticlotting agents (heparin, glycoprotein IIb/IIIa inhibitors, clopidogrel) with aspirin improves outcomes in acute coronary syndromes, while exacerbating this bleeding tendency.

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastric ulcers, and, in patients treated with warfarin, the risk of bleeding from a peptic ulcer is increased almost threefold by concomitant use of a NSAID.

Indomethacin, piroxicam, and probably other NSAIDs antagonize the antihypertensive effects of β-adrenergic receptor blockers, diuretics, ACE inhibitors, and other drugs. The resulting elevation in blood pressure ranges from trivial to severe. This effect is not seen with aspirin and sulindac but has been found with cyclooxygenase-2 inhibitors (celecoxib, rofecoxib).

Torsades de pointes during administration of QT-prolonging antiarrhythmics (quinidine, sotalol, dofetilide) occur much more frequently in those patients receiving diuretics, probably reflecting hypokalemia. In vitro, hypokalemia not only prolongs the QT interval in the absence of drug but also potentiates drug block of ion channels that results in QT prolongation. Also, some diuretics have direct electrophysiologic actions that prolong QT.

The administration of supplemental potassium leads to more frequent and more severe hyperkalemia when potassium elimination is reduced by concurrent treatment with ACE inhibitors, spironolactone, amiloride, or triamterene.

The pharmacologic effects of sildenafil result from inhibition of the phosphodiesterase type 5 isoform that inactivates cyclic GMP in the vasculature. Nitroglycerin and related nitrates used to treat angina produce vasodilation by elevating cyclic GMP. Thus, coadministration of these nitrates with sildenafil can cause profound hypotension, which can be catastrophic in patients with coronary disease.

Sometimes, combining drugs can increase overall efficacy and/or reduce drug-specific toxicity. Such therapeutically useful interactions are described in chapters dealing with specific disease entities, elsewhere in this text.

ADVERSE REACTIONS TO DRUGS

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these untoward effects often present diagnostic problems because they can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Major advances in the investigation, development, and regulation of drugs ensure in most instances that drugs are uniform, effective, and relatively safe and that their recognized hazards are publicized. However, prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials, and the selected nature of these patients, rare adverse effects may not be detected prior to a drug's approval, and physicians therefore need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized adverse events. Often, these adverse reactions are rare, such as hematologic abnormalities, arrhythmias, hepatitis, or renal dysfunction. In these cases, often (but inappropriately) labeled "idiosyncratic," elucidating underlying mechanisms can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure. National adverse reaction reporting systems, such as those operated by the U.S. Food and Drug Administration (suspected adverse reactions can be reported online at *http://www.fda.gov/medwatch/report/hcp.htm*) and the Committee on Safety of Medicines in Great Britain, can prove useful. The publication or reporting of a newly recognized adverse reaction can in a short time stimulate many similar such reports of reactions that previously had gone unrecognized.

Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients led to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. These examples further reinforce the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

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Editors

DENNIS L. KASPER, MD
William Ellery Channing Professor of Medicine, Professor of Microbiology and Molecular Genetics, Harvard Medical School; Director, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston

ANTHONY S. FAUCI, MD
Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda

DAN L. LONGO, MD
Scientific Director, National Institute on Aging, National Institutes of Health, Bethesda and Baltimore

EUGENE BRAUNWALD, MD
Distinguished Hersey Professor of Medicine, Harvard Medical School; Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston

STEPHEN L. HAUSER, MD
Robert A. Fishman Distinguished Professor and Chairman, Department of Neurology, University of California San Francisco, San Francisco

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